UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:	:	
	:	**17-MD-2767 (PAE)**
MIRENA IUS LEVONORGESTREL-RELATED	:	**17-MC-2767 (PAE)**
PRODUCTS LIABILITY LITIGATION (NO. II)	:	
	:	
This Document Relates To All Actions	:	

PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE EXPERT TESTIMONY OF LAURA PLUNKETT, PhD,

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PRELIMINARY STATEMENT

Dr. Plunkett is a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist, and principal of a consulting company called Integrative Biostrategies, LLC. Expert Report 1 ("Plunkett Rpt."), attached as Ex. A. Dr. Plunkett received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. *Id.* Dr. Plunkett is board-certified as a Diplomate of the American Board of Toxicology, and she has taught pharmacology and toxicology at the undergraduate and postgraduate levels. *Id.* As a pharmacologist, her work has been directed towards understanding the biologic mechanisms of drug actions, including both the therapeutic and toxic effects of drugs. Dr. Plunkett has done a great deal of work on projects related to regulation of human drug products, including examining the risks associated with exposure to hormones and the risks associated with altered hormonal status in women. *Id.* at 2. Dr. Plunkett is also an expert in pharmacokinetics, including the different pharmacokinetics of drugs when they are administered by routes other than oral ingestion, e.g., dermal, inhalation, subcutaneous, intraperitoneal, and intra-vaginal. *Id.* at 2-3.

In forming her opinions for this litigation, Dr. Plunkett used standard, reliable methods that she applies in all of her work as a pharmacologist and toxicologist. *Id.* at 4; *see also* January 19, 2018 Deposition of Laura Plunkett, Ph.D. ("Plunkett Tr.") at 384:5-23, 390:11-391:1.[1] Dr. Plunkett applied a weight of the evidence assessment to the information that she studied and reviewed. A weight of the evidence assessment involves evaluating individual studies and determining what the studies describe when considered as a whole. *Id.* Weight of the evidence methodology is used as part of regulatory decision-making by regulatory and scientific bodies

[1] For the Court's convenience, relevant excerpts from Dr. Plunkett's deposition transcript have been pulled and marked as Ex. B.

such as the FDA, the U.S. Environmental Protection Agency (EPA), the U.S. Occupational Safety and Health Administration (OSHA), the World Health Organization (WHO), and the International Agency for Research and Cancer (IARC).[2] Dr. Plunkett also performed a Bradford Hill analysis. *Id.* at 26-35. In performing her weight-of-the-evidence analysis, Dr. Plunkett examined the Mirena product labeling, internal Bayer documents related to the pharmacokinetics, pharmacology and toxicology of Mirena, the scientific literature related to the benefits and risks of levonorgestrel products, as well as the FDA regulations that govern the development and marketing of human prescription drug products. Dr. Plunkett was trained in the use of weight of the evidence assessments as part of her undergraduate, graduate and postdoctoral work in pharmacology and toxicology, as well as while working as a consultant in human health risk assessment. *Id.* Considering all of the relevant information, it is Dr. Plunkett's opinion, to a reasonable degree of scientific certainty, that exposure to Mirena can be a substantial contributing factor to development of PTC/IH in women, and that LNG exposure can cause PTC/IH. *Id.* at 26.

FACTUAL BACKGROUND

Levonorgestrel (LNG) is a potent synthetic progestin.[3] *See* Defendants' Brief ("Dfts. Br.") at 2, FACTUAL BACKGROUND (The Mirena IUD "consists of a T-shaped plastic frame with a reservoir that releases LNG, a progestogen steroid hormone.") Although Mirena *generally* releases lower daily doses of LNG than other levonorgestrel-containing contraceptives, and – according to Bayer – it "mainly localizes in the patient's uterine cavity" (Dfts. Br. 2), the resulting serum level of LNG, and resultant profile of systemic side effects in individual women,

[2] *See* Plunkett Rpt. at 5.

[3] Progestin is one of many names for a class of synthetic sex hormones (such as LNG) derived from testosterone, with the desired effect of progesterone (the natural female steroid hormone responsible for both preventing and maintaining pregnancy). Other names for this group of hormones include progestogens (*e.g.*, Dfts. Br. 2) and gestagens (*e.g.*, Ex. C, Fotherby K. Levonorgestrel. Clin Pharmacokinet. 28 (3): 203-15. 1995 ("1995 Fotherby").

is far from simple. First, "[m]etabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG–containing contraceptive products." Ex. D, Mirena [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; October 2015 (hereinafter, "2015 Mirena Label"). Serum (*i.e.*, systemic) LNG levels vary greatly both inter- and intra-individually, regardless of the method of administration. *See generally* Ex. C, 1995 Fotherby.

The expected side-effect profile of Mirena compared to other LNG-containing contraceptives is further complicated and magnified by pharmacological principles of steroid hormone activity. Steroid hormones such as LNG induce or inhibit various activities in the human body – both desired contraceptive action, and adverse effects such as acne – by binding at steroid hormone receptors within cells at the target organs. *See generally* Ex. E, A. Phillips, D.W. Hahn and J.L. McGuire, Relative binding affinity of norgestimate and other progestins for human sex hormone-binding globulin, Steroids 55(8): 373-375 (1990). Concurrently, sex hormones also bind with varying affinity to the transport proteins albumin and sex hormone binding globulin (SHBG). *Id.* Prevailing principles of cellular biochemistry provide that the fraction of the sex hormone bound to SHBG is thereby "occupied" and incapable of binding to receptors, and hormonal activity is therefore limited to the degree of binding to SHBG. *See, e.g.*, November 21, 2017 30(b)(6) Deposition of Birte Hofmann, ("Hoffman 30(b)(6) Tr."), attached as Ex. F, at 294:11-294:22. Therefore, the free (*i.e.*, unbound) fraction of the sex hormone is highly relevant to predicting its resulting activity. Ex. G, Mendel CM, The free hormone hypothesis: a physiologically based mathematical model, Endocrine Rev 16: 232-274, 1989; *see also* Ex. H, MIR_JR_00183776, 05/11/2004 Statement on the use of FLI (free levonorgestrel

index) for comparison of different estrogen/LNG combinations[4] ("Based on these facts, the unbound or free fraction of LNG are considered to be more important for any comparison between different estrogen/LNG combinations."). Prevailing principles of cellular biochemistry provide that the fraction of the sex hormone bound to SHBG is thereby "occupied" and incapable of binding to receptors, and hormonal activity is therefore limited to the degree of binding to SHBG. *See, e.g.*, Ex. F, Hoffman 30 (b)(6) Tr. at 294:11-294:22.

While Mirena contains *only* LNG, nearly every LNG-containing oral contraceptive marketed in the United States contains an estrogen component, commonly in the form of ethinyl estradiol (EE). *See*, U.S. Department of Health and Human Services, FDA Drug Database search results, Norgestrel.[5] "Administration of [LNG] alone markedly reduces serum SHBG levels and causes a concomitant decrease in SHBG-bound levonorgestrel"; however, "when the same dose [is] given with ethinyl estradiol, the reverse occur[s], i.e., a minor increase in SHBG and SHBG-bound levonorgestrel[.]" Ex. C, 1995 Fotherby, at 207. Correspondingly, when administered alone, more LNG is "free", and therefore capable of binding to steroid hormone receptors, and inducing or inhibiting hormonal activity. Therefore, although Mirena use *generally* "results in lower circulating levels of LNG than do other LNG-containing contraceptives" (Dfts. Br. 2-3), its capacity to induce hormonal action is not necessarily – or simply – dose-dependent. Ex. I, Ewies AA, Levonorgestrel-releasing Intrauterine System – The discontinuing story. *Gynecol Endocrinol.* October 2009; 25(10): 668-673, at 669 ("There are large variations among different studies as regards the mean LNG concentrations after administration of the same dose of LNG, and there is insufficient data to show whether there is a correlation between dose and serum concentrations.")

[4] Dr. Christian Zurth served as Senior Pharmacokinetics Expert in Women's Healthcare for Bayer and its predecessors until 2012. He was deposed as a fact witness in this litigation on November 29, 2017.
[5] Search executed March 14, 2018. Available at https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Finally, "[a]n ideal progestin should achieve a progestational response when given at a low concentration but elicit an androgenic response only at a high concentration." Ex. J, Darney PD, The Androgenicity of Progestins. Am J Med. 1995; 98 (suppl 1A):104S-110S, at 1105S. Because LNG binds significantly to *every* steroid hormone receptor with varying affinity – particularly to the androgen receptor – it exhibits substantial hormonal activity even at a low concentration. *Id.*; *see also* Juchem & Pollow, Am. J. Obstet. Gynecol. 163: 2171-2182, 1990; Kuhl, Drugs 51: 188-215, 1996; Stanczyk[6] et al., Endocrine Rev. 34: 171-208, 2013; Sitruk-Ware, Hum. Reprod. Update 12: 169-178, 2006; Africander et al., Steroids 76: 636-652, 2011. Additionally, Bayer's own expert report on the toxico-pharmacological documentation to the Mirena NDA states: "LNG is not a pure progesterone agonist. It has a low, but substantial affinity to the androgen receptor and the mineralocorticoid receptor, and to some transport proteins." Ex. K, MIR_PIEU-R_00377654

Even Population Council scientist, Dr. Regine Sitruk-Ware,[7] has described this chemical process in the medical literature. *See e.g.*, Ex. L, Sitruk-Ware, R. New progestagens for contraceptive use. Hum Reprod. 2006; 12(2):169-178 ("[t]he effects of progestins are related to interactions not only with the progesterone receptor (PR) but also with other steroid hormone receptors. Some progestins interact with the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR) or the mineralocorticoid receptor (MR).") Binding to these receptors "may either induce transactivation of a steroid receptor or prevent activation. In the target organ, the balance between the receptor coactivators and corepressors recruited by a progestin determines whether the overall effect of the molecule will be agonistic or antagonistic." *Id.* Therefore, the common adverse effects of LNG that are included on the Mirena

[6] Dr. Frank Stanczyk has served as a paid consultant for Bayer Healthcare.
[7] Population Council was the original sponsor of the Mirena New Drug Application ("NDA"), later transferred to Bayer Healthcare. Dr. Sitruk-Ware has also served as a paid consultant for Bayer Healthcare.

label are directly attributable to these hormone-receptor interactions,[8] as acknowledged by even Bayer's own paid consultants and researchers.

Unsurprisingly, Bayer researchers have attempted to develop a "New Progestin" for contraceptive use, designed for superior "dissociation of local vs. systemic" side effects. Ex. M, U.S. Patent Application Publication No. US 2015/0065472 Al (43) (published Mar. 5, 2015), at p. 11 of 13. *See also* Ex. N, MIR_CH-R_00085086, 09/22/2010 Meeting Minutes, at -5089 ("The dissociation of local vs. systemic progestogenic activity provided by BAY 1007626 is expected to address liabilities of Mirena or LCS as outlined by research"); Ex. O, MIR_HC-R_00013317, 2010 Masterplan Project Description, at -3319 (Project Rationale. "Undesired effects of MIRENA® concern systemic effects such as ovarian cyst formation, acne, and breast tenderness. These side effects are due to the systemic availability of Levonorgestrel.") Clearly, as opined by Dr. Plunkett and as Bayer well knows, the circulating levels of LNG provided by Mirena, and Mirena's corresponding side effect profile, are far from *de minimis.*

STANDARD OF REVIEW

In the interest of brevity, Plaintiffs will not set forth a detailed discussion of the legal standard in this Memorandum. Plaintiffs respectfully refer the Court to the legal standard set forth in detail in Plaintiffs' Omnibus Motion and hereby incorporate that Omnibus Motion into this Memorandum. In short, Federal Rule of Evidence 702 requires that expert testimony be "not only relevant, but reliable." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590 (1993). To be reliable, "[t]he subject of an expert's testimony must be 'scientific . . . knowledge.'" *Id.* at 589-90. Under *Daubert*, "an expert need not base his opinion on the best possible evidence, but upon 'good grounds, based on what is known.'" *Deutsch v. Novartis Pharms. Corp.*, 768 F.

[8] For example, acne and ovarian cysts (> 5% reported in clinical trials) are evidence of androgenic activity. *See* Ex. C at 15.

Supp. 2d 420, 453 (E.D.N.Y. Mar. 8, 2011) (quoting 509 U.S., at 590). "Rule 702 codifies a liberal admissibility standard and '[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence.'" *Id.*, at *426 (quoting 509 U.S. at 596). *See also Beastie Boys v. Monster Energy Co.*, 983 F. Supp. 2d 369, 377 (S.D.N.Y. 2014).

ARGUMENT

I. Dr. Plunkett's Weight of the Evidence Methodology Is Reliable and Well-Applied

Court's within the Second Circuit have "liberally construed expert qualification requirements." *In re Methyl Tertiary Butyl Ether ("MTBE") Prods. Liab. Litig.*, No. 00-CV-1898, 2008 WL 1971538, at *5 (S.D.N.Y. May 7, 2008) (internal quotation marks omitted). An expert's analysis "need not be perfect to be received in evidence—it need only rest on a reliable foundation that is relevant to the task at hand." *Hart v. Rick's Cabaret Int'l, Inc.*, 60 F. Supp. 3d 447, 467 (S.D.N.Y. 2014).

In reaching her conclusions, one of the tools Dr. Plunkett employs is a weight of the evidence assessment. Weight of the evidence assessment involves examining individual data and then reaching a conclusion based on the evidence when viewed as a whole. In other words, conclusions are drawn based on the big picture—not just a single piece of evidence. A weight of the evidence assessment in science is analogous to a totality of the circumstances analysis in law. When asked during her deposition about her methodology, Dr. Plunkett testified:

> So to me the weight of the evidence is a methodology or a tool that scientists use in order to evaluate scientific information, and it can be done in a variety of context. I use weight of the evidence in my regulatory work. When I'm putting together a dossier on a compound to describe information for a – for regulators such as the FDA, I put together parts of a safety assessment, for example. I use it in litigation as well when I'm doing my causation analysis . . . . It's essentially gathering all the information you can that are relevant to a question you're trying to answer. So in a case like this . . . I gathered . . . all of the information I could find publicly available as well as what was referred to in

> the labeling or referred to within the FDA submission. And I looked at what that information said based on weighing that information across the quality of data. You evaluate different studies based on whether or not they're peer-reviewed or not, whether or not the information is – has statistical analysis attached to it, things like that.

Plunkett Tr. 384:9 – 385:16. Defendants' criticisms of Dr. Plunkett for allegedly citing to "speculative" literature suggest that they do not fully understand how a weight of the evidence analysis works. *See* Dfts. Br. at 15. It is sound methodology to consider and weigh *all* of the relevant evidence, including evidence that has not been proven as scientific fact. *See, e.g. General Electric Co. v. Joiner*, 522 U.S. 136, 153-55 (1997) (Stevens, J. dissenting) ("It is not intrinsically unscientific for experienced professionals to arrive at a conclusion by weighing all available scientific evidence—this is not the sort of 'junk science' with which *Daubert* was concerned . . . ."). Obviously, in a weight of the evidence analysis, the expert gives the most deference to scientific literature that has been proven or nearly proven. That does not mean, however, that a piece of literature should be excluded simply because the author exhibited some reservations about its conclusions. Bayer criticizes this reliable and well-accepted methodology by making atomistic arguments, attacking specific details in Dr. Plunkett's report and citations. This type of argument is inappropriate and urges an improper analysis of expert testimony. *See Milward v. Acuity Specialty Prods. Group*, 639 F.3d 11, 23 (1st Cir. 2011). In *Milward*, the First Circuit identified and rejected this type of piecemeal analysis. *Id.* "At times, the court's error in excluding Dr. Smith's testimony derived from a mistake in its understanding of the weight of the evidence methodology employed by Dr. Smith. The court treated the separate evidentiary components of Dr. Smith's analysis atomistically, as though his ultimate opinion was *independently* supported by each." *Id.* (emphasis in original).

Bayer attempts to hold Dr. Plunkett's testimony to a higher standard than is required for admission. She is not required to have tested whether Mirena use causes PTC/IH. Under

Daubert, whether or not something has been tested and its potential error rate is known are only two of four factors to take into consideration. *Daubert,* 509 U.S. 579, 592-93. Dr. Plunkett used the tested and accepted weight of the evidence method in reaching her conclusion and it is a permissible basis for expert testimony under *Daubert*. *See Milward*, 639 F.3d at 18-19 ("The fact that the role of judgment in the weight of the evidence approach is more readily apparent than it is in other methodologies does not mean that the approach is any less scientific . . . . No serious argument can be made that the weight of the evidence approach is inherently unreliable"); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584 (D.N.J. 2002) ("[T]he weight-of-the-evidence methodology has been used, in a non-judicial context, to assess the potentially carcinogenic risk of agents for regulatory purposes. The existence and maintenance of standards controlling the technique's operation when used for regulatory purposes is informative here. The EPA's Guideline for Carcinogenic Risk Assessment specifically sets forth the types of information that should be considered and the standards that information must meet. [Guidelines for Carcinogen Risk Assessment, 51 Fed. Reg. 33992, 33996 (September 24, 1986)].")

In an effort to undermine Dr. Plunkett's weight of the evidence methodology, Bayer attacks Dr. Plunkett's Biological Gradient Opinion by pointing to evidence that Dr. Plunkett allegedly "ignores." Dfts. Br. 6. Dr. Plunkett acknowledges that total LNG serum levels in combined oral contraceptive users is on average higher than total levels in Mirena users. *Id.* Conveniently, Bayer fails to mention that Dr. Plunkett went on to explain why a comparison in LNG serum levels between combined oral contraceptive users and Mirena users is flawed. Dr. Plunkett went on to say:

> But again, this is a different product because it's . . . a combination product . . . this is, again, an apples to oranges comparison now because now you've got the effect of estrogen and progestins on levels of binding protein, so it's a little bit more complex. This calculation – well, not calculation. This paper introduces additional complexities,

> which is again why I've tried to focus on the single products, the single hormone products, when you're making a comparison, such as the Norplant product.

Plunkett Tr. 95:2-16. Bayer points to LNG serum levels in users of combined oral contraceptives to argue that LNG could not possibly cause PTC/IH in Mirena users. But as Dr. Plunkett stated during her deposition, Mirena is a progestin-only product, whereas combined oral contraceptives contain estrogen. In conducting her weight of the evidence assessment, Dr. Plunkett gives more weight to Norplant than combined oral contraceptives because Norplant is more similar to Mirena than combined oral contraceptives. Specifically, the only active ingredient in Norplant is LNG[9]. It would be unreasonable for Dr. Plunkett to give more consideration to combined oral contraceptives than a product such as Norplant[10]. In fact, analyzing combination hormonal contraceptives would only muddy the waters, which apparently is exactly what Bayer is attempting to do[11].

Dr. Plunkett relies on a substantial body of evidence to support her opinions. Bayer's mere disagreement with these opinions does not render these opinions inadmissible.[12]

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[9] Interestingly, Bayer also attacks Dr. Plunkett's discussion of Norplant as a helpful analogy in the Mirena/PTC analysis. Apparently, Bayer wants Dr. Plunkett to consider other contraceptive products, but only if it leads her away from her ultimate causation opinions.

[10] A comparison between Mirena and LNG COCs is especially misplaced. As the Court is aware from Dr. Conrad Johanson's report, the hormonal homeostasis is disrupted by the introduction of LNG without an estrogen component, ultimately leading to development of PTC. While a full discussion of this neurological mechanism of LNG induced PTC is beyond the scope of this Response, it is sufficient to say that comparing COCs, which contain an estrogen component, to Mirena is not helpful or relevant.

[11] A further example of Bayer's inappropriately atomistic argument is found in its criticism of Dr. Plunkett's consideration of adverse event case reports. Dr. Plunkett was very clear in her deposition that a single case report is not sufficient to prove causation. However, she has not merely cited a single case report, she has cited a substantial body of evidence in support of her causation opinion. Case reports are a part of the body of evidence, and Dr. Plunkett has relied on them as such. *See, e.g.*, 124:18-125:1. Despite Bayer's arguments, just because a single piece of evidence does not prove causation does not mean that it should be disregarded, especially when it is part of a wider body of evidence that supports causation.

[12] While Bayer, at times, seems to request wholescale exclusion of Dr. Plunkett's opinions, its Motion sets forth no argument relating to several of Dr. Plunkett's opinions. Specifically, Bayer makes no specific attack on Dr. Plunkett's opinions related to the intra-individual and inter-individual variability of free levels of LNG or the androgenic nature of LNG.

II. Bayer's Claim That Dr. Plunkett's Opinion Should Be Excluded Because It Does Not Satisfy the *Daubert* Factors Misconstrues *Daubert* Jurisprudence.

Although Fed. R. Evid. 702 sets forth specific criteria for the district court's consideration, the *Daubert* inquiry is fluid and will necessarily vary from case to case. *Amorgianos v. Amtrak*, 303 F.3d 256, 266 (2d Cir. 2002); *see also In re M/V MSC Flaminia*, No. 12-cv-8892 (KBF), 2017 U.S. Dist. LEXIS 119146, at *171-72 (S.D.N.Y. July 28, 2017). The Supreme Court has identified a number of factors bearing on reliability that district courts may consider, such as (1) whether a theory or technique "can be (and has been) tested," *Daubert*, 509 U.S. at 593; (2) "whether the theory or technique has been subjected to peer review and publication," *id*.; (3) a technique's "known or potential rate of error," and "the existence and maintenance of standards controlling the technique's operation," *id*. at 594; and (4) whether a particular technique or theory has gained "general acceptance" in the relevant scientific community," *id. See also Fed. Deposit Ins. Corp. v. Suna Assocs., Inc.*, 80 F.3d 681, 687 (2d Cir. 1996) (discussing *Daubert* factors); Jack B. Weinstein & Margaret A. Berger, Weinstein's Federal Evidence § 702.05[2][a], at 702-66 to 702-72.2 (Joseph M. McLaughlin ed., 2d ed. 2002) (listing factors for the district court's consideration identified in *Daubert* and its progeny). Contrary to Bayer's urging, these factors do not constitute a "definitive checklist or test." *Daubert*, 509 U.S. at 593. Rather, "the inquiry envisioned by Rule 702 is . . . a flexible one," *id*. at 594, and "the gatekeeping inquiry must be tied to the facts of a particular case," *Kumho Tire v. Carmichael*, 526 U.S. 137, 150 (1999).

Further, experts need not conduct studies of their own in order to opine on a topic; a review of other studies and scientific literature can be enough to qualify experts to testify and to make that proposed testimony reliable. *See McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1042-43 (2d Cir. 1995); *see also Cedar Petrochemicals, Inc. v. Dongbu-Hannong Chem. Co.*, 769 F.

Supp. 2d 269, 284 (S.D.N.Y. 2011) ("Experts need not have actually collected the data on which they base their conclusions in order to be credible."); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 282 (E.D.N.Y. 2007).

Dr. Plunkett's opinions meet the admissibility requirements of *Daubert* because she gives well-supported, scientific opinions that will assist the trier of fact in understanding how LNG—the active ingredient in Mirena—can cause PTC/IH. In formulating her opinions, Dr. Plunkett used standards and methods that she applies in her day-to-day work as a pharmacologist, toxicologist, and regulatory specialist. Dr. Plunkett's methodology, including her risk assessment and weight of the evidence analysis, is well-accepted in scientific and regulatory communities.

Bayer argues for exclusion of Dr. Plunkett's entire report because it "does not satisfy any of the enumerated *Daubert* factors." Dfts. Br. 3. Bayer claims that 1) Dr. Plunkett has never tested her opinions; 2) in the absence of testing, there is no known error rate; 3) Dr. Plunkett has never shared her opinion about Mirena and PTC/IH with anyone other than Plaintiffs' attorneys; and 4) Dr. Plunkett's opinion that Mirena causes PTC/IH is not generally accepted. *Id.* Yet, it is well-established that the *Daubert* factors are neither exclusive nor some type of rigid checklist. In support of its claim that Dr. Plunkett has never tested her opinions, Bayer cites part of her deposition transcript in which she was asked if she had ever administered LNG to an animal or human. *Id.* (citing Plunkett Tr. 55:22 – 56:8). Dr. Plunkett responded that she has not. *Id.* It is absurd to argue that administration of LNG to an animal or human is a prerequisite to giving an opinion on the causal relationship between Mirena and PTC/IH. Dr. Plunkett is giving an opinion on the causal relationship between a drug and a disease, and there is no legal requirement that Dr. Plunkett personally administer that drug before she gives an opinion.

Bayer also strains to undermine Dr. Plunkett's opinions by pointing to Dr. Plunkett's lack of publication on Mirena and PTC/IH. *Id* at 4. However, lack of publication does not make an opinion per se unreliable. Indeed, if publication was a requirement, none of Bayer's proffered experts would be qualified to give opinions, either. For example, when asked whether she had ever published anything on PTC/IH, Bayer's expert Dr. Hewitt stated, "I have not published any article on IIH, IH, or pseudotumor cerebri." Hewitt Tr. at 119:17-18. Likewise, when asked whether any of the numerous published articles listed in her CV related to IIH, Bayer's expert Dr. Gossett replied, "I have not published anything on intra – idiopathic intracranial hypertension." Gossett Tr. at 47: 5-22. To argue that Dr. Plunkett is not qualified to give an opinion on the relationship between Mirena and PTC/IH exposes Bayer to the same criticism. The conclusions regarding Mirena and PTC/IH are relatively new and are still developing, so it is not surprising that the tendered experts in this litigation have yet to publish on the topic.

Finally, Bayer claims that Dr. Plunkett's opinions should be excluded under *Daubert* because they are not generally accepted. A reading of the Supreme Court's opinion in *Daubert*, however, makes clear that "[n]othing in the text of [Fed. R. Evid. 702] establishes 'general acceptance' as an absolute prerequisite to admissibility." *Daubert*, 509 U.S. at 588. Quite the opposite, in fact, as *Daubert*'s progeny shows. A mechanism need not be definitively established or generally accepted to be admissible. Likewise, "'[t]hat the mechanism remains unknown does not mean that the one proposed by the [plaintiffs' experts] is not widely accepted as plausible.'" *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 198 (S.D.N.Y. 2009) (citing *In re Neurontin Mktg. Sales Practices and Prods. Liab. Litig*., 612 F. Supp. 2d 116, 149 (D. Mass. 2009) (finding that biologic plausibility supported opinion on causation despite the fact that there was 'robust debate in the scientific community' on the proposed mechanism); *In re PPA Prods.*

Liab. Litig., 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003) ("The fact that the mechanism remains unclear does not call the reliability of the opinion into question."). *Deutsch v. Novartis Pharms. Corp.*, 768 F. Supp. 2d 420, 438, 2011 U.S. Dist. LEXIS 22755, *47-48 (citing *Fosamax*, 645 F. Supp. 2d at 198).

In forming her opinions, Dr. Plunkett studied and examined relevant data, then carefully drew her conclusions based on the totality of the available evidence. Dr. Plunkett's opinions were formed in light of her more than thirty years of experience in pharmacology, toxicology, and pharmacokinetics. When questioned about her methodology, Dr. Plunkett responded that it is "a standard method scientists use." Plunkett Tr. 386:8-9. Further, Dr. Plunkett confirmed that "[r]isk assessment is a standard tool used by pharmacologists and toxicologists when they are trying to understand the benefits and risks associated with a drug." *Id*. at 388:19-24 (quoting Plunkett Rpt. at 4). Additionally, Dr. Plunkett testified that the use of principles such as dose response and exposure in her Mirena safety assessment is a commonly accepted methodology in pharmacology and toxicology. Plunkett Tr. 390:11-18. Dr. Plunkett utilized reliable and well-accepted methods to reach her opinions. Her opinions are not, as Bayer so disingenuously suggests, the product of subjective and conclusion-driven methodology.

III. Dr. Plunkett's Opinions Regarding Norplant Are Relevant and Reliable

Dr. Plunkett's opinions on Norplant are relevant and sufficiently supported by a reliable foundation. *See Campbell v. Metro. Prop. & Cas. Ins. Co.*, 239 F.3d 179, 184 (2d Cir. 2001). Bayer seeks to exclude these opinions because they undermine its argument that other Plaintiffs' experts' opinions are incomplete because they have not considered whether Norplant, another LNG-only product, can cause PTC/IH. Interestingly, Bayer attacks Plaintiffs experts both when

they consider Norplant and when they do not consider it enough. See, e.g., Memorandum of Law in Support of Defendants' Motion to Exclude the Expert Testimony of Philip Darney, M.D.

Dr. Plunkett offers the opinion that toxic effects observed in patients exposed to Norplant would be expected to occur in patients taking other LNG drug products, including Mirena. Plunkett Rpt. 7. Bayer moves for exclusion of Dr. Plunkett's opinions on Norplant because Bayer contends those opinions are irrelevant. Dfts. Br. 4-5. Contrary to what Bayer alleges, Dr. Plunkett's opinions regarding Norplant are relevant to this litigation for several reasons. Norplant is a subdermal hormonal contraceptive implant that was developed by Defendants prior to Mirena. Norplant contains the same active ingredient as Mirena—LNG—and it contains warnings for PTC. *See* Norplant Product Label, attached as Exhibit __. As Dr. Plunkett testified: "the closest comparison product would be the subdermal implants based on the way that the drug is released over time, long term in the body versus a daily oral dose with one single bolus." Plunkett Tr. 22:6-11.

It is undisputed that Dr. Plunkett did not conduct a full causation analysis between Norplant and PTC/IH. *See* Plunkett Tr. 31:23-32:9. But Dr. Plunkett did analyze the pharmacokinetic properties of Norplant and FDA documents to conclude that Norplant has been linked to PTC/IH. *Id.* at 33:2-10. Dr. Plunkett's opinion regarding Norplant is relevant to general causation because if LNG can cause adverse effects in Norplant users, it is likely that LNG can cause similar effects in Mirena users. The jury should be allowed to consider the effects of a similar product that contains the same active ingredient as the product at issue in this litigation.

As stated above, Dr. Plunkett reviewed sufficient literature and information to conclude there is a causal relationship between Norplant and PTC. The analogy to Mirena that follows is just one piece of evidence relied upon by Dr. Plunkett to reach her ultimate causation opinions.

Again, Dr. Plunkett analyzed the totality of all evidence, not just a single piece of evidence. Bayer has chosen only to attack Dr. Plunkett's opinions on a micro-level, because the argument for exclusion falls apart at the macro-level.

IV. Dr. Plunkett's Bradford Hill Analysis is Relevant and Reliable

In reaching her opinions regarding Mirena and PTC/IH, Dr. Plunkett also conducted a Bradford Hill analysis. The Bradford Hill factors are routinely considered by scientists when trying to determine whether a drug is the cause of a particular effect in humans. *See* Hill, A.B. 1965 *Proc. Royal Soc. Med.* 58:295-300, attached as Ex. P. It is reasonable and scientifically valid to utilize a Bradford Hill analysis in determining whether Mirena can cause PTC/IH. *See, e.g., Deutsch v. Novartis Pharms. Corp.*, 768 F. Supp. 2d 420, 455-57 (2d. Cir. 2011). Contrary to Bayer's assertion, a clear-cut association is not required for a Bradford Hill analysis to be appropriate. Further, there is no single Bradford Hill criterion that must be fulfilled for the analysis to be valid. Hill at 299. Specifically, Sir Bradford Hill states:

> What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non.*

Id. (emphasis in original).

Dr. Plunkett conducts a Bradford Hill analysis, in which she considers two peer-reviewed epidemiological studies, numerous case reports, and a host of medical literature that provide support for the causal mechanism she proposes. Bayer has criticisms and responses to Dr. Plunkett's Bradford Hill Analysis. Def. Memorandum at 19-20. These criticisms and responses can and should be presented and argued at trial. However, this is not a proper reason to exclude these opinions. Ultimately, Dr. Plunkett's Bradford Hill analysis and Bayer's criticisms of this Bradford Hill analysis are for the jury to consider. *See Daubert*, 509 U.S. at 506 ("vigorous

cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof enable jury to weigh shaky but admissible evidence); *Ambrosini v. Labarraque*, 101 F.3d 129, 141 (D.C. Cir. 1996) (credibility of expert and persuasiveness of study were for fact finder). The use of Bradford Hill is not novel or speculative; Bradford Hill is well-established in the scientific community, and Dr. Plunkett's analysis should be admitted.

V. Dr. Plunkett's Androgen Mechanism Is A Biologically Plausible Mechanism of PTC/IH

"Biologic plausibility is a judgment about whether an agent *plausibly* could cause a disease, based on existing knowledge about human biology and disease pathology." *Fosamax*, 645 F. Supp. 2d 164, 181 (citing Michael D. Green et al., Reference Guide on Epidemiology at 388 in Federal Judicial Center, Reference Manual on Scientific Evidence (2d Ed. 2000) (emphasis added)); *See also Zwillinger v. Garfield Slope Hous. Corp.*, 1998 U.S. Dist. LEXIS 21107, *56-57, 1998 WL 623589 (citing Reference Manual on Scientific Evidence at 201) ("A scientifically valid opinion . . . typically requires an analysis of whether there is a 'biologically plausible theory' by which the disease can be related to the alleged chemical exposure . . .").

Dr. Plunkett gives the opinion that increased androgenic activity in patients taking LNG drug products, including Mirena, is a biologically plausible mechanism for PTC. Plunkett Rpt. 32. This opinion is not "purely speculative" as Bayer contends. Dr. Plunkett formulated this opinion after considering the pharmacodynamic properties of LNG, the active ingredient in Mirena, and the scientific literature describing a relationship between PTC and androgens. *Id*.

Dr. Plunkett's androgen mechanism is not something she came up with out of thin air. LNG is a potent synthetic progestin. Frequently, pharmacologists point to the binding and agonistic properties of a drug to predict pharmacological effects consistent with those properties. *See, e.g.*, Ex. Q, Africander et al., *Molecular mechanisms of steroid receptor- mediated actions*

by synthetic progestins used in HRT and contraception, 76 STEROIDS 636, 636 (abstract) (2011) ("Since many progestins bind not only to the progesterone receptor, but also to the glucocorticoid, androgen, mineralocorticoid, and possibly the estrogen receptors, it is plausible that synthetic progestins exert therapeutic actions as well as side-effects via some of these receptors."); *see also* Defendants' Expert Report of Dr. William Jusko at 2 ("In particular, we routinely measure the receptor binding of corticosteroids, assess subsequent genomic, biochemical, physiologic, and pharmacologic responses to these drugs, and develop mechanistic mathematical models to account for these processes."). Further, Dr. Plunkett cites to numerous studies that lend support to her opinions. Specifically, Dr. Plunkett's report reads:

> Although the exact pathophysiologic mechanism responsible for inducing PTC in humans is not known, there are several plausible mechanisms that have been discussed in the scientific literature. One of these mechanisms involves the actions of the endocrine system. The pathogenesis of PTC is complex and likely multi-factorial, although endocrine systems appear to play key roles (Mollan *et al.* 2016). In a recent paper, the role of androgens in PTC was described (Klein *et al.* 2013). The authors [found] that increased levels of androgens but not estrogen, follicle-stimulating hormone, luteinizing hormone, or prolactin, was associated with an earlier age of onset of PTC in women. PTC has been linked to polycystic ovarian syndrome, PCOS (Glueck *et al.* 2005), a condition that is characterized by high levels of circulating androgens (citation omitted), which is further support for a role of androgens in the pathogenesis of PTC. In a recent abstract, an androgen signature was identified in patients with idiopathic intracranial hypertension, *i.e.*, pseudotumor cerebri (O'Reilly *et al.* 2017). An androgen signature for PTC has been discussed by other scientists as well (Hornby *et al.* 2016; Kempegowda *et al.* 2016).

Plunkett Rpt. 31-32. Even Bayer's own internal documents support the conclusions regarding the androgenic nature of LNG. *See* Ex. K, MIR_PIEU-R_00377654

Bayer cites *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986 (8th Cir. 2001) in its argument that discussing LNG's androgenic properties is "making a leap" that amounts to an excludable *ipse dixit* opinion. Dfts. Br. at 17-18. This misrepresents both *Glastetter* and the *Joiner* opinion, which underlies the *Glastetter* opinion. *Glastetter*, 252 F.3d at 990, *see also*

General Electric Co. v. Joiner, 522 U.S. 136 (1997). In *Glastetter*, an excluded expert speculated without any supporting evidence that the drug at the center of that case would act like other drugs in its class of medical substances. *Id.* That could not be further from the scenario at hand. Dr. Plunkett's report discussed LNG's documented androgenic effects on the human body. Plunkett Rpt. at 7, 11-13, 31-33. The androgenic and mineralocorticoid impact of LNG is thoroughly established and does not require a leap. *Id.* at 11-12. This is nothing like the "generic assumption" excluded in *Glastetter* because this behavior is documented with LNG in particular and is known and accepted by Bayer. *Id.* at 11-12.

Bayer additionally cites *In re Accutane*, a case from the Middle District of Florida, which is not binding authority in this Court. While Defendants may argue that biological plausibility is not proof of causation, it is certainly evidence of causation: "[w]hen biological plausibility exists, it lends credence to an inference of causality." *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007). Further, Dr. Plunkett's finding of biological plausibility is only one facet of her Bradford Hill analysis. Plunkett Report at 31. Dr. Plunkett's testimony is also based on the strength of the association, consistency of the association, specificity of the injury, temporality of the injury in relation to the exposure, evidence of a dose-response effect, coherence with what is known about the disease, studies regarding the relationship, and analogy to other drug's injury profiles. Plunkett Report 25-35. Bayer misrepresents Dr. Plunkett's analysis and misrepresents the level of proof required for biologic plausibility. Finally, Bayer sinks to the level of semantic arguments in attacking Dr. Plunkett, highlighting words like "possible", "speculate", "might", and "hypothesis" from literature cited by Dr. Plunkett. Dfts. Br. at 15.

It is again important not to fall into the atomistic trap that Bayer sets. Bayer urges the Court to exclude the totality of Dr. Plunkett's opinions based on a piecemeal analysis of specific citations. As stated previously, this approach loses sight of the totality of the evidence supporting Dr. Plunkett's opinions and is inappropriate in the *Daubert* context. *Milward*, 639 F.3d at 23. Second, the semantic argument that Bayer asserts is patently incorrect. As the United States Supreme Court stressed in *Daubert*: "it would be unreasonable to conclude that the subject of scientific testimony must be 'known' to a certainty; arguably, there are no certainties in science . . . 'Indeed, scientists do not assert that they know what is immutably 'true' – they are committed to searching for new, temporary, theories to explain, as best they can, phenomena.'" *Zuchowicz*, 870 F. Supp. at 20 (quoting *Daubert*, 509 U.S. at 590) (quoting Brief for American Association for the Advancement of Science et al. as *Amici Curiae* 7-8). Thus, "[s]cience is not an encyclopedic body of knowledge about the universe. Instead, it represents a *process* for proposing and refining theoretical explanations about the world that are subject to further testing and refinement." *Id.* (emphasis in original).

The language of science is different than that of law. It is inappropriate to discount scientific evidence merely because it uses language that does not express the correct legal standard for causation. It is important to also point out that Dr. Plunkett's opinions are stated to a reasonable degree of scientific certainty, which is the appropriate standard for an expert witness. Dr. Plunkett examined the relevant scientific evidence to conclude that androgen activity is a biologically plausible mechanism for PTC/IH. Dr. Plunkett does not contend that androgen activity is the *only* mechanism by which PTC/IH occurs; she simply states it is a biologically plausible mechanism by which Mirena can cause PTC/IH. The jury should be allowed to consider and weigh this testimony.

CONCLUSION

Wherefore, Plaintiffs respectfully request that this honorable Court deny Bayer's Motion to Exclude the Expert Testimony of Laura Plunkett, Ph.D., DABT.

Dated: March 15, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 15, 2018, I served all counsel of record with the foregoing via this Court's CM/ECF System, which will provide notice of filing to all counsel of record.

/s/ Martin D. Crump
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